

A Biologist's View of Gibbs' Contributions

Harold J. Morowitz

*Department of Molecular Biophysics and Biochemistry,
Yale University, New Haven, Conn.*

ABSTRACT

Five examples illustrate the particular orientation given by Gibbs' thermodynamics or statistical mechanics to approaches to contemporary research in the life sciences.

Approaching the hundredth anniversary of Gibbs' work on heterogeneous equilibrium, and trying to assess Gibbs' influence on biology arouses feelings of nostalgia. I must therefore introduce my topic with a few personal notes. I first learned of Gibbsian thermodynamics in Leigh Page's course on Introduction to Theoretical Physics, where I was introduced to the Ψ , χ , ζ functions of the Professor. So while the rest of the world talked of enthalpies, free energies, and the rest, we contented ourselves with the original 1875 nomenclature. This quaint approach was not so strange, for Page came to Yale in 1900 and spent the first 3 years of his career in a department in which Gibbs was still an active contributor. Thus, I feel myself a member in a line of direct microcanonical succession from the master himself.

These psychological ties go deeper, for on several occasions when my unease over a scientific problem rendered me peripatetic I have wandered from the Gibbs laboratory where I work to the nearby Grove Street Cemetery to pause before the Gibbs family gravesite and wonder where this modest man drew the inspiration to penetrate problems with such clear and brilliant insight. However, lest we get maudlin, let us turn from the man to his work.

Gibbsian concepts have so penetrated modern biological and biochemical thought that any attempt to survey their impact would go far beyond the limits of this presentation. Rather, we will

focus attention on 5 examples from contemporary life science, where the particular orientation given by Gibbs to some aspect of thermodynamics or statistical mechanics has motivated a significant approach to some biological area.

One of the most fertile papers in modern molecular biology has been "Equilibrium Sedimentation of Macromolecules in Density Gradients" by Meselson et al. (1957). These studies opened the way to the separation of isotopically labeled nucleic acids on the basis of density. It provided immediately successful analytical and separatory techniques which have been among the principle tools in the study of both prokaryotic and eukaryotic genetic material. The application of this technique quickly led to an understanding of the semiconservative replication of bacterial DNA (Meselson and Stahl, 1958). Much of our detailed understanding of the nature of DNA replication rests on experiments using equilibrium density gradients.

The theory of density gradients follows from the generalization of the chemical potential set forth by Gibbs in his study of heterogeneous equilibrium. Thus the theory section of the density gradient paper begins:

"II Quantitative Relations

The total potential of any component at equilibrium in a closed system at constant temperature must be uniform through the system. In a centrifugal

field this requirement results in the rigorous condition.³

$$M_i(1 - \bar{v}_i\rho(r))\omega^2rdr - \sum_k \frac{\partial\mu_i}{\partial C_k} dC_k = 0$$

where M_i , \bar{v}_i , μ_i , C_i are molecular weight, partial specific volume, partial molar (Gibbs) free energy and concentration of the i th component."

Reference 3 in the above quotation is to T. Svedberg and K.O. Pedersen, *The Ultracentrifuge* (1940). Interestingly enough, Pedersen in his chapter on sedimentation equilibrium in the reference just cited has a footnote which states: "For the thermodynamical deduction of equations for sedimentation equilibrium compare, for instance: The Scientific Papers of J. W. Gibbs I, 144-50 (London 1906); etc, etc." The reference in Gibbs is to a section called "The Conditions of Equilibrium for Heterogeneous Masses under the Influence of Gravity." The equation given by Meselson et al. (1957) follows directly from the treatment given by Gibbs with the substitution of the centrifugal acceleration ω^2r for the gravitational acceleration. We have thus traced the direct link from the cesium chloride gradients for DNA back to the underlying theory as set forth in 1875.

The second example I would like to give has provided a central theme to modern theoretical ecology and has formed the underlying assumption of a number of studies. The paper I refer to is "A Statistical Mechanics of Interacting Biological Species" by Edward Kerner (1957). Kerner is a physicist and an unabashed Gibbsian who has used the insights of statistical mechanics to attempt to deal with biological problems of such high order of complexity that detailed treatment seems to be impossible. Kerner's approach has stimulated theoretical studies in cell biology (Goodwin, 1963), neurophysiology (Cowan, 1972), and complex chemical systems (Kerner, 1964).

Kerner's reliance on Gibbs' statistical mechanics is most clearly seen in the

following quotation from the 1957 paper:

"To proceed at once from the starting Volterra equations is therefore plainly desirable, if not absolutely necessary. Now, the statistical mechanics customary in physics, that form of it elaborated by J. W. Gibbs (1902), rests on the Hamiltonian form of the equations of motion only weakly, almost incidentally, the role of Hamilton's equations being to make evident the two corner stones of the statistical development: Liouville's theorem and energy conservation. It will appear that the initial Volterra equations readily admit a Liouville's theorem and a universal constant of the "motion" somewhat like the Hamiltonian of classical dynamics; and then a statistical analysis of some simplicity, parallel to Gibbs', becomes feasible. Herewith we find a lesson from physics as well as to physics, an example of how much broader is the statistical side of statistical mechanics than the mechanics which calls it into existence."

With the above in mind Kerner proceeds to recast the Volterra equations into equations of motion and then to form a "Gibbs ensemble of biological associations." For such an ensemble he proves "Liouville's theorem of conservation of density in phase." The analogy is carried forward to the introduction of a number of new parameters which have provided stimulus to ecological thought.

The statistical ideas of Gibbs stressed by Kerner had already entered biology by an entirely alternate route. Norbert Wiener in his book *Cybernetics* (1948) opened up a whole new paradigm on the role of feedback systems in biology. Chapter II of that book deals extensively with the work of Gibbs and Henri Lebesque. Wiener wrote:

"Gibbs, mathematician that he was, always regarded mathematics as ancillary to physics. Lebesque was an analyst of the purest type, an able exponent of the extremely exacting modern stand-

ards of mathematical rigor; . . . Nevertheless, the work of these two men forms a single whole in which the questions asked by Gibbs find their answers, not in his own work, but in the work of Lebesgue."

Wiener proceeds to a detailed discussion of the ergodic hypothesis which serves as an introduction to his discussion of information. Thus the cybernetic and information theory approaches in biology are also touched by a Gibbsian influence.

Gibbsian statistical mechanics, insofar as it provided part of the foundation of information theory, has had a broad and difficult task to delineate influence on contemporary biology. The information measure of Shannon, which relates closely to the entropy measure of statistical mechanics, has been widely used by biologists in a series of problems ranging from evaluating primary sequence in biopolymers to behavioral studies dealing with the rate of information processing in humans (Quastler, 1953).

The next example is much more experimental in outlook, yet illustrates the power of one of the concepts from the discussion of heterogeneous equilibrium. For a number of years the detailed study of membrane structure has been a problem of great difficulty. The obvious chief role of the plasma membrane is to separate the aqueous interior of the cell from the aqueous exterior. Such separation is necessary to accord an integrity to the interior, so that a degree of regulation is possible. Since all membranes contain appreciable amounts of amphiphilic molecules such as phospholipids, these substances were some of the logical candidates for the non-aqueous phase. The very notion of phase in this sense goes back to the section of the heterogeneous equilibrium paper called "On Coexistent Phases of Matter."

The notion that membranes consist largely of bimolecular leaflets of polar lipid molecules with interior lipid and exterior polar groups has been one of the popular membrane models since late

in the 1920's. However, proof was lacking. In 1969 Stein and coworkers (Stein et al., 1969) examined purified membranes of *Acholeplasma laidlawii* by differential scanning calorimetry and observed a distinct heat absorption peak which they took to be associated with a phase transition in the membrane bilayer. They extracted the membrane lipids, formed synthetic bilayers from them, and observed that these materials yielded differential calorimetric scanning patterns similar to the membrane.

In our laboratory we have repeated Stein's results and have been able to utilize Dr. Sturtevant's highly sensitive calorimeter to demonstrate the phase transition in whole living cells (Melchior et al., 1970). Engelman (1970) used the phase transition to measure the change of bilayer thickness during the phase transition by the technique of x-ray diffraction. The phase change and change of thickness aided in interpreting the diffraction pattern. This series of phase change measurements has now made it very clear that most of the lipids in mycoplasma membranes are in the bimolecular leaflet configuration.

Our final case study involves an area where the answers are not yet completely in—the attempts to develop a nonequilibrium thermodynamics and statistical mechanics appropriate to biology. An example of this approach is the book "Nonequilibrium Thermodynamics in Biophysics" by Aharon Katchalsky and Peter F. Curran (1965). They start with the introduction of the Gibbs equation

$$dU = TdS - PdV + fdl$$

$$+ \psi de + \sum_{i=1}^k \mu_i dn_i + \dots$$

which is strictly applicable to equilibrium reactions and extend it to near equilibrium by the assumption of local equilibrium. They note "the range of applicability of the Gibbs equation cannot be specified on *a priori* grounds, and the justification of its use rests in the final analysis, on the validity of the

results obtained. On the basis of this criterion, many irreversible processes of interest can be treated using Eq. (7-2) as a starting point." Using this approach, the authors develop an approach to membrane and transport processes which has been influential in the current study of these problems in biology.

The possible treatment of nonequilibrium cases has been pursued in statistical mechanics as well as thermodynamics. E. T. Jaynes in his paper "Information Theory and Statistical Mechanics" (1957) has extended the statistical mechanics of Gibbs to make contact with the information theory of Shannon and Weaver (1964) and has provided a basis for extending the ensemble approach into the nonequilibrium domain. Jaynes has written:

"The mathematical facts concerning maximization of entropy were pointed out long ago by Gibbs. In the past, however, these properties were given the status of side remarks not essential to the theory and not providing in themselves any justification for the methods of statistical mechanics. The feature which was missing has been supplied only recently by Shannon in the demonstration that the expression for entropy has a deeper meaning, quite independent of thermodynamics. This makes possible a reversal of the usual line of reasoning in statistical mechanics. Previously, one constructed a theory based on the equations of motion, supplemented by additional hypotheses of ergodicity, metric transitivity, or equal *a priori* probabilities, and the identification of entropy was made only at this end, by comparison of the resulting equations with the laws of phenomenological thermodynamics. Now, however, we can take entropy as our starting concept, and the fact that a probability distribution maximizes the entropy subject to certain constraints becomes the essential fact which justifies use of that distribution for inference."

In the Jaynes formalism the maximization of entropy is the equivalent to

making the maximally noncommittal statement with respect to missing information. It is an extension of Laplace's principle of insufficient reason to any case where constraints can be formulated and a probability distribution is a reasonable way to formulate the problem. It is therefore applicable to any situation where ensembles and ensemble averages are appropriate for the formulation of a problem.

We have attempted to use the Jaynes approach in 3 studies aimed at developing non-equilibrium statistical techniques for biological problems (Rider and Morowitz, 1968; Morowitz, 1971; Corbet and Morowitz, 1972). While such approaches are in their early stages, they do indicate the potential power of the ensemble technique in problems extending beyond the original equilibrium mechanics treated by Gibbs.

In retrospect it is surprising to realize the number of crucial areas in modern biological thought where concepts originally set forth by Josiah Willard Gibbs have come to maturity. It requires an event such as this symposium to force us to focus attention on the fruits of the labors of a modest genius such as Gibbs.

As a biologist, one can only lament that Gibbs failed to make a contribution to the gene pool. While he left no children, he has numerous intellectual heirs who share the huge wealth of ideas left deposited in his writings.

References Cited

- Corbet, A., and H. J. Morowitz. *Phys. Rev. A*, 6, 2298, 1972.
- Cowan, J. in *Proceedings of the Sixth IUPAP Conference on Statistical Mechanics*, University of Chicago Press, 1972.
- Engelman, D. M. *J. Mol. Biol.* 47, 115, 1970.
- Goodwin, B. *Temporal Organization in Cells*. Academic Press, 1963.
- Jaynes, L. T. *Phys. Rev.* 106, 620, 1957.
- Katchalsky, A., and P. Curran. *Non-Equilibrium Thermodynamics in Biophysics*. Harvard University Press, 1965.
- Kerner, E. H. *Bull. Math. Biophys.* 19, 121, 1957.
- Kerner, E. H. *Bull. Math. Biophys.* 26, 333, 1964.
- Melchior, D. L., H. J. Morowitz, J. M. Sturtevant, and T. Yow Tseng. *Biochim. Biophys. Acta* 219, 114, 1970.

Meselson, M., F. W. Stahl, and J. Vinograd. P.N.A.S. (U.S.) 43, 581, 1957.
 Meselson, M., and F. W. Stahl. P.N.A.S. (U.S.) 44, 671, 1958.
 Morowitz, H. J. p. 37-41 in *Chemical Evolution and the Origin of Life*. Buvet, R. and C. Ponnamperna. North Holland Publishing Co., 1971.
 Quastler, H. *Essays on Information Theory in Biology*. University of Illinois Press, 1953.
 Rider, K., and H. J. Morowitz. *J. Theoret. Biol.* 21, 278, 1968.

Shannon, C. E., and W. Weaver. *The Mathematical Theory of Communication*. University of Illinois Press, 1964.
 Stein, J. M., M. E. Tourtellotte, J. C. Reuert, R. N. McElhaney, and P. L. Rader, P.N.A.S. (U.S.). 63, 104, 1969.
 Svedberg, T., and K. O. Pederson. *The Ultracentrifuge*. Oxford, 1940.
 Wiener, N. *Cybernetics*. John Wiley and Sons, 1948.

Centennial of Gibbs' Thermodynamics — Concluding Remarks

R. E. Gibson

Director Emeritus, Applied Physics Laboratory, The Johns Hopkins University

The President's reference to the 18 years that have elapsed since I held the position he now occupies is one of two recent instances that have reminded me of the rapid passage of time. The other occurred a few days ago when, in preparation for this symposium, I looked into the volumes of Gibbs' collected works that I first studied some 45 years ago. Although I had remembered vividly the pleasure that came from following the closely knit arguments and ingenious graphical demonstrations that led him from two very simply stated but pregnant general principles to elucidate phenomena and laws covering a vast area of physical chemistry, I found with some dismay that much of the content seemed unfamiliar, forgotten over years of preoccupation with other matters. Only handwritten marginal notes assured me that once I had studied these papers assiduously. The papers tonight brought alive again the realization that those articles published—mostly in the Transactions of the Connecticut Academy approximately a century ago—are still a rich mine of scientific gold.

Let me base these concluding remarks on a passage from a memorial biography¹ written in 1903 by H. A. Bumstead, a student and colleague of Gibbs, and later Professor of Physics and Director for many years of the Sloane Physics Laboratory at Yale:

"Although he disregarded many of the shibboleths of the mathematical rigorists, his logical processes were really of the most severe type; in power of deduction, of generalization, in insight into hidden relations, in critical acumen, utter lack of prejudice, and in the philosophical breadth of his view of the object and aim of physics, he has had few superiors in the history of the sciences; and no student could come in contact with this serene and impartial mind without feeling profoundly its influence in all his future studies of nature."

Through the exercise of these *logical processes*, Gibbs left a legacy of elegant instruments of thought such as the concept of the chemical potential (often very loosely called the "Free Energy" or "Partial Free Energy") together with

¹American Journal of Science, Series 4, Vol. XV, September 1903. Reprinted in "The Collected Works of J. Willard Gibbs, Vol. I, Longmans, Green & Co., New York, 1928.